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## **Appeasing the carotid body after chronic intermittent hypoxia**

Julian F.R. Paton

School of Physiology, Pharmacology & Neuroscience, Biomedical Sciences, University of  
Bristol, Bristol BS8 1TD, England.

Corresponding author:

Professor Julian F.R. Paton

School of Physiology, Pharmacology & Neuroscience

Biomedical Sciences

University of Bristol

Bristol BS8 1TD

England.

Tel: -44 (0)117 331 2275

Fax: -44 (0)117 331 2288

Email: [Julian.F.R.Paton@Bristol.ac.uk](mailto:Julian.F.R.Paton@Bristol.ac.uk)

Running title: *Targeting the carotid body in sleep apnoea*

## Commentary

I recall vividly a conversation with the late Professor C. John Dickinson DM. FRCP, ARCO (Professor of Medicine and Chairman of the Department of Medicine at St Bartholomew's Hospital, London 1975-1992) who remarked that in the majority of cases cardiovascular pathology occurred at night whilst asleep. John's great hypothesis was that a shortage of oxygen to the brain, due to high cerebrovascular resistance, triggered hypertension, and that was worsened by the diurnal falls in blood pressure further compromising cerebral perfusion. Clearly, such a mechanism would be thoroughly agonised during sleep disordered breathing.

Sleep disordered breathing occurs in approximately one in five males and one in ten women aged between 50–70 years<sup>1</sup>. With an increasing incidence of between 14-55% over the last two decades<sup>1</sup>, sleep disordered breathing is growing into a huge clinical and economic problem. Associated with sleep disordered breathing is narcolepsy, cardiovascular disease including heart failure and hypertension, autonomic imbalance, baroreceptor re-setting and inflammation. The causes of sleep apnoea are partly dependent on whether the apnoeas are obstructive or central in origin but many patients have a combination of both.

Continuous positive airway pressure has been shown to reduce peripheral chemosensitivity (as seen as a reduction in the hypoxic ventilatory response<sup>2</sup>) and abolish hypopneas and apneas in patients with *obstructive* sleep apnoea<sup>3</sup>. However, the associated hypertension, which is found in at least 50% of cases, is typically not ameliorated<sup>3</sup>. Central sleep apneas are controlled using adaptive servo ventilation: a recent study by Cowie et al. in heart failure patients with reduced left ventricular ejection fraction, used adaptive servo-controlled inspiratory pressure and expiratory positive airway pressure (SERVE-HF<sup>4</sup>). Unexpectedly, all-

cause mortality and cardiovascular mortality were significantly *higher* relative to the control group. Thus, alternative strategies for the treatment of sleep disordered breathing and associated cardiovascular disease are needed and the paper recently published by Del Rio et al.<sup>5</sup> is most timely. They used a rat model of chronic intermittent hypoxia, which generated modest hypertension and showed that once the hypertension was fully established selective removal of the carotid body chemoreceptors bilaterally normalised arterial pressure. This parallels the classic earlier work of Eugene Fletcher<sup>6</sup> who showed that in rats transection of the carotid sinus nerves prevented hypertension in response to chronic intermittent hypoxia. But Del Rio's study documents new information of high clinical relevance. Importantly, and for the first time, they show that performing the intervention *after* the hypertension had developed was successful, suggesting that the carotid bodies are essential for the maintenance of hypertension accompanying chronic intermittent hypoxia, and not just its development. The significance of this from a clinical perspective is that patients' obviously only present when they express the symptom. Thus, a treatment strategy that can alleviate an established hypertension has important clinical implications. Additionally, the authors used radio-telemetry to allow high fidelity blood pressure to be measured definitively in conscious rats; earlier studies used tail cuff or indwelling chronic catheters that can both cause stress and easily confound blood pressure data. They also provide evidence that autonomic balance is restored to the heart, which provides a plausible explanation for the reduction in arrhythmias induced by the chronic intermittent hypoxia<sup>5</sup>. Baroreceptor reflex function, which was depressed by the chronic intermittent hypoxia, was markedly improved post-carotid body ablation. Rescuing the baroreceptor reflex by improving its reflex gain and lowering its set-point should not be underestimated as a potential mechanism for both the anti-hypertensive effect and restoring autonomic balance

after carotid body removal. Recent human trials have stimulated the carotid sinus as an effective treatment in some hypertensive patients<sup>7</sup>. The improvement in baroreflex function may come about through a reduction in peripheral chemoreceptor drive as this is known to have an antagonistic action, probably within the brainstem.

Mechanistically, chronic intermittent hypoxia sensitises the peripheral chemoreceptors – so called hyperreflexia. This is portrayed by the augmented ventilatory response to hypoxia in the Del Rio et al study<sup>5</sup>. As reported by McBryde et al.<sup>8</sup> in the spontaneously hypertensive rat, this hyperreflexia was accompanied by elevations in ongoing tonic drive emanating from the carotid body. The study by Del Rio et al.<sup>5</sup> shows that increased carotid body afferent tone must also exist and likely explains the enhanced tidal volume at rest and the presence of hypertension. These data are consistent with the recently proposed peripheral afferent activation hypothesis of hypertension<sup>9</sup>, where sensitisation and tonicity of afferent sensors, such as the carotid body, muscle/renal afferents, drive autonomic imbalance contributing to sympathetic excess and the ensuing hypertension (Figure).

Clinically, the question is whether carotid body ablation would be a safe way to alleviate sleep disordered breathing (and the associated cardiovascular diseases) or might the apneic events worsen? The answer to this question might depend on whether the apneas are of central or obstructive in origin. There are some other considerations to mention: first, are carotid chemoreceptors involved in the initiation of an apneic event caused by over active peripheral chemoreception leading to a period of hyperventilation induced hypocapnia that de-stabilises the respiratory rhythm generator (Figure). Second, are the carotid bodies important for the arousal from the apnea? If carotid bodies were ablated would there be

any compensation from central chemoreceptors? Since carotid bodies provide excitatory drive to the central chemoreceptors (Figure) it may be imperative to assess the activity of them and their apneic threshold before irreversible ablation of carotid bodies. Third, it is not easy to gauge the importance of carotid body chemoreceptors in respiratory dysfunction based on current animal models. In the Del Rio et al<sup>5</sup> study there is no evidence that chronic intermittent hypoxia induced breathing irregularities and, although proposed originally as a model of sleep apnea<sup>6</sup>, this model has its limitations for understanding respiratory arrhythmias and sleep apnoea *per se*. Do we need to add chronic intermittent hypoxia to an existing model of heart failure or hypertension to better mimic the human condition? Animal models displaying apneas such as the Rett syndrome mice, in which methyl CpG binding protein 2 is knocked out, might better lend themselves as a model for understanding apneas and strategies for their rescue. Indeed, our data point strongly to excitability of expiratory neural elements causing post-inspiratory apnea<sup>10</sup>. There are two messages here: (i) there is a need for more detailed assessment of respiration – it is all too easy to measure inspiration only but the apnea is often caused by a dysfunction/prolongation of expiration (post-inspiration and stage II expiration, Figure; <sup>10</sup>); (ii) it is the strength of the expiratory neurone coupling to sympathetic neurones that appears exaggerated contributing to sympathetic over activity in hypertension<sup>11</sup> including chronic intermittent hypoxia<sup>12</sup> (Figure); (iii) post-inspiratory activity also drives upper airway adductors that could contribute to obstructive apneas (Figure). Thus, future studies should consider measuring expiratory as well as inspiratory activity.

Ultimately, evidence for a role for carotid body ablation or its modulation in sleep disordered breathing pathologies will need to come from human studies and these have

begun. Carotid body resection has been used as a treatment for systolic heart failure<sup>13</sup> and drug resistant hypertension<sup>14</sup>. In both these studies direct evidence for reductions in muscle sympathetic activity was found. Regarding sleep disordered breathing, the data are limited in heart failure to a case study where unilateral carotid body resection was performed<sup>13</sup>. This resulted in a reduction in central sleep apneas. In hypertensive patients where one carotid body was removed there were no significant changes in the apnea-hypopnea index<sup>14</sup>. All told, it may be that the type of apnoea (central vs obstructive) will be important for determining both the efficacy and appropriateness of adopting carotid body ablation/modulation as a therapeutic approach for the treatment of sleep disordered breathing. Nevertheless, Del Rio et al.<sup>5</sup> have clearly shown the potential clinical benefit of carotid body denervation in a model of chronic intermittent hypoxia for the restoration of autonomic balance; this now adds to the clinical benefit of carotid body ablation/denervation seen in both animals and humans with heart failure<sup>13, 15</sup> and hypertension<sup>8,14</sup>.

Important questions remain: why does sensitisation occur in the carotid body and what are the molecular mechanisms that cause a sustained afferent drive in sleep disordered breathing and cardiovascular diseases? Could a single mechanism exist across multiple disease states that explains this aberrant carotid body tone or are the mechanisms responsible disease-specific? Is it possible that there are different mechanisms within the carotid body driving breathing versus autonomic pathologies perhaps based on distinct subsets of glomus cells connected to separate central reflex pathways (Figure) as we suggested previously<sup>16</sup>. The chronic intermittent hypoxic model has shed light on numerous potential mechanisms<sup>17</sup>. Important for translation is that any antagonist targeting identified

mechanisms of carotid body sensitisation must be relatively selective and not induce unwanted side effects. Future research efforts should attempt to pharmacologically target the carotid body to appease its excitability, which would avoid the irreversibility issue of denervation or ablation, but preserve its physiological function. This remains an important future challenge but based on the Del Rio et al.<sup>5</sup> study it is likely to be a most clinically productive strategy.

To conclude, the Del Rio et al. study<sup>5</sup> on the role of the carotid bodies for the maintenance of the hypertension induced by chronic intermittent hypoxia in rats adds further credence to the rapidly emerging and topical opinion that this chemoreceptive site is contributing substantially to cardiovascular pathology and, therefore, opens future opportunities for therapeutic targeting, especially because it lies outside the central nervous system.

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## Figure legend

A theoretical, simplified schematic of the connections of the carotid body glomus cells to the cardiovascular and respiratory networks within the medulla oblongata. As portrayed by the colour coding, we hypothesise that glomus cells are connected separately via the nucleus of the solitary tract (NTS) to dedicated reflex pathways, as previously suggested<sup>16</sup>.

We also propose that carotid body excites selective groups of medullary neurones regulating cardiovascular and respiratory functions. In particular, we highlight the physiological response (kinesiology; dashed arrows): (i) the central chemoreceptive neurones in the retrotrapezoid nucleus (RTN) that have onward connections to the pre-sympathetic neurones of the rostroventrolateral medulla (RVLM) and the ventral respiratory column (VRC) neurones to power the respiratory oscillator. We infer that RTN excitability depends in part on input from the glomus cells. (ii) the post-inspiratory (post-insp) neurones as drivers of sympathetic activity via the RVLM, cardiac vagal pre-ganglionic vagal motoneurones and laryngeal adductors located in the nucleus ambiguus (NA); (iii) inspiratory (insp) VRC neurones driving pre-ganglionic vagal bronchoconstrictors located in the NA. Pathology (solid lined arrows) results from increased sensitisation/tonicity of the carotid body contributing to elevated chemical loop gain resulting in hyperventilation induced hypocapnia; this depresses the RTN, destabilises the respiratory pattern generator during sleep causing central apnoea (CSA), hypoxia, sympathoactivation, hypertension, cardiac arrhythmias (due to excessive simultaneous co-activation of cardiac sympathetic and cardiac vagal drives). With an excess glomic drive to glottal adductors and bronchioles this may also agonise obstructive sleep apnoea (OSA). These apneas cause intermittent hypoxia and hypercapnia providing positive feedback to the carotid body that may contribute to their sensitisation and aberrant tonicity. Del Rio et al.<sup>5</sup> showed how disconnecting the

carotid body afferent nerves running through the petrosal ganglion abolished the established hypertension and cardiac arrhythmias induced by chronic intermittent hypoxia. These data and the schematic single out the carotid body as a putative therapeutic target for a number of cardiovascular, respiratory and pulmonary diseases.

